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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,963	05/31/2005	Ryoichi Kawamura	KAWAMURA69	6392

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EXAMINER	
DUTT, ADITI	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,963	KAWAMURA ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 11 December 2006 has been entered in full.

Election/Restrictions

2 Applicant's election without traverse of Group II, represented by claims 8-17, drawn to a method for ameliorating a neurotransmission dysfunction disease by administering a medicament comprising a selenocysteine containing protein, in the reply filed on 11 December 2006 is acknowledged.

3. Claims 1-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11 December 2006.

4 Applicant's election of myasthenia gravis as the neurotransmission dysfunction disease, and SEQ ID NO: 4 as the peptide sequence, will be considered for examination.

Specification

5. The disclosure is objected to because of the following informalities:

A) Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "METHOD FOR IMPROVING NEUROTRANSMISSION FAILURE USING A NOVEL AGENT".

Appropriate correction is required.

B) The abstract of the disclosure is objected to because of the lack of proper and sufficient content to support the claimed invention.

A new abstract in compliance with M.P.E.P. 608.01(b) is required.

C) Internet address:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, for example, page 6, line 21; page 8, line 2; IDS, Cite No. AQ). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Objections

6. Claims 8-17 are objected to because of the following informalities:

a) Claim 8-12 depend from claims 1-5 respectively, which recite a non-elected invention. Appropriate correction is required.

b) Claims 13-17 have the following typo 'acetlylcholine' instead of 'acetylcholine'.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhancing acetylcholine receptor function in rats, and accelerating synaptic formation in vitro, using the full-length sequence of selenoprotein P (SeP), does not reasonably provide enablement for ameliorating any neurotransmission dysfunction disease, by administering SeP, a C-terminal peptide of SeP, its partial sequences, or a series of peptides comprising deletions and substitutions, recited in the claims, to a patient in need thereof, for example having abnormality in synaptic formation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

8. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

9. The claims are drawn to a method for ameliorating any neurotransmission dysfunction disease (for example, myasthenia gravis), by administering a medicament comprising selenocysteine-containing protein (SeP), peptide consisting of SeP or a series of such peptides, C-terminal peptide of SeP comprising amino acids 260-362 of SeP, peptide having SEQ ID NO: 4, or an amino acid sequence with deletions, substitutions or partial sequences of the above peptides, to a patient having an abnormality in synaptic formation, or in acetylcholine receptor function, or in neurotic activity by nitrogen monoxide, (claims 8-17).

10. With respect to claim breadth, the standard under 35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification (see MPEP 2111 [R-1]), which states that claims must be given their broadest reasonable interpretation.

11. "During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt,* 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad

interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly that is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)".

12. As such, the broadest reasonable interpretation of the claimed method is for ameliorating any neurotransmission dysfunction disease, comprising administering any selenocysteine-containing protein consisting of full-length SeP, its C-terminal peptides, or a series of peptides comprising partial sequence, additions, deletions or substitutions of above peptides to a patient in need thereof.

13. The specification of the instant application teaches that selenocysteine-containing proteins are plasma proteins, which encompass full-length SeP of SEQ ID NO: 1, and other diverse proteins derived from SeP, such as a C-terminal peptide, that are involved in the inhibition of cell-death (page 14, lines 15-19; page 8, lines 12-16). The specification also teaches that, SeP induces synaptic formation and differentiation to neurons after 3 days of culture of NG108-15 hybridoma cells (page 21-24, Example 1, Table 1, Figure 1). The specification further teaches that injections of SeP and pilocarpine (acetylcholine receptor agonist) to ICR male mice, results in an enhanced induction of convulsion, thereby suggesting an effect of SeP on accelerating the muscarinic acetylcholine receptor function (pages 24-26, Example 2, Table 2). However, the specification does not provide any evidence or sound scientific reasoning that the limited information presented in the disclosure can be directly extrapolated to

methods of ameliorating any neurotransmission dysfunction disease, comprising administering SeP, a C-terminal peptide of SeP, or a series of peptides comprising deletions, substitutions or partial sequences of SeP, to a patient in need thereof, such as having an abnormality in synaptic formation.

14. Relevant literature teaches that selenocysteine-containing proteins, such as glutathione peroxidase, SeP etc., comprise selenium, incorporated as the amino acid selenocysteine (Chen and Berry, Jour Neurochem. 86: 1-12, 2003). The literature also teaches that SeP is synthesized and secreted by the liver, and consists of 2-4 isoforms in the rat and human plasma (Hill and Burk, Biomed Environ Scie. 10: 198-208, 1997, page 206, last para; Mostert , V. Arch. Biochem. Biophys. 376: 433-438, 2000, page 434, "Isoforms of SeP"; Chen and Berry, page 6, "Selenoprotein P"). The literature further teaches that SeP mRNA is expressed in tissues such as kidney, brain, pancreas etc., and that SeP demonstrates antioxidant properties during inflammation and other diseases (Mostert , V., page 436, column 2, para 3; page 437). Using in vitro studies, Chen and Berry teaches that selenoprotein P could be essential for neuronal survival due to its ability to supply selenium in cell cultures (page 7, column 1, para 3). Furthermore, SeP administration in an aging mouse model (Klotho), resulted in improving decreased motor function (Masaki et al. European Patent Application No. EP 1 374887 A1, dated 2 January, 2004; pages 8-9, Examples 3, 5). However, the specification does not teach any methods or working examples to indicate that all possible SeP, C-terminal peptide sequence, or a series of

peptide sequences comprising deletions or substitutions or partial peptide sequences, that would ameliorate any neurotransmission dysfunction disorder by administration to a patient having abnormality in synaptic formation, for example. Undue experimentation would be required of the skilled artisan to determine such. Furthermore, the specification does not teach functional or structural characteristics of the fragments and variants of SeP recited in the claims other than the polypeptide comprising the full-length amino acid sequence of SeP (SEQ ID NO: 1). It is not clear from the relevant pre and post-filing date literature as to what regions of the SeP sequences or the maximum length of the sequences are essential for biological activity. Thus, undue experimentation would be required of the skilled artisan to identify the precise structural characteristics of SeP fragments and variants showing amelioration of neurotransmission dysfunction activity. Undue experimentation would also be required of the skilled artisan to identify and administer a medicament comprising all possible SeP peptides.

15. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various

sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the SeP proteins which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

16. Furthermore, in vitro conditions do not necessarily mimic in vivo conditions, which involve communication and complex interactions within/between neurons producing different neurotransmitters, to elicit a response. In vitro experiments such as that described in the instant application (Example 1), are vastly different from in vivo assays, both physiologically or biologically, and in predictability of success, and thus would entail undue experimentation by a skilled artisan (See *Maas*, 9 USPQ2d 1746). There is also little guidance in the specification, as to whether the medicament is capable of crossing the blood brain barrier, thereby entailing undue experimentation to determine the effectiveness of the medicament. For example, the art demonstrates that a high concentration of SeP is associated with the vascular endothelial cells that form the inner layer of the blood brain barrier (BBB), thereby raising doubts on the transportation of injected SeP accross the BBB (Chen and Berry, page 8, column 2, para 2). The skilled artisan would not be able to predict that all variants and fragments of SeP administration would result in agents crossing the blood brain barrier, relocating to the target region of the brain and subsequently treating all possible neurotransmission dysfunction disorders. It is also well known in the art neurotransmission dysfunction diseases such as myasthenia gravis (The Merck Manual, Sc 14, Ch. 183, web site), Alzheimer's Disease (Halliday et al Clin Exp Pharmacol Physiol 27: 1-8, 2000), and Huntington's Disease (Feigin et al., Curr Opin Neurol 15: 483-489, 2002), are proven to be recalcitrant to treatment. Finally, the difficulty of in vivo treatment for

neurotransmission dysfunction is acknowledged in the instant specification that states that, "neurotransmitters and their receptors have many types and diverse actions such as excitement and restraint to cells and thus adverse side effects tend unexpectedly to occur" (page 7, lines 18-22). As the precise mechanism of action of SeP in neurotransmission dysfunction diseases including myesthenia gravis are yet to be fully uncovered, the success of treatment would be unpredictable, thus the invention would entail undue experimentation by a skilled artisan. Additionally, one skilled in the art would not be able to predict from the instant specification that all possible neurotransmission dysfunction diseases would be ameliorated by administration of all possible peptide sequences of SeP to patients in need thereof. Undue experimentation would be required to determine such. Undue experimentation would also be required of the skilled artisan to determine the optimal dosage and type of administration of the agent.

17. Due to the large quantity of experimentation necessary to generate the infinite number of variants of SeP peptide, and to administer the medicament comprising the peptides for therapeutic use to treat any neurotransmitter dysfunction disorder; the lack of direction/guidance presented in the specification regarding the same; the complex nature of the invention; the unpredictability of administering the SeP peptide in vivo and the state of the prior art which establishes the utilization of the animal models to study/treat degenerative disorders; and the breadth of the claims which fail to recite any structural or

functional limitations - undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

18. Claims 8, 10-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

19. Claims 8, 10-15 and 17, are drawn to a method for ameliorating any neurotransmission dysfunction disease (for example, myasthenia gravis), by administering a medicament comprising a peptide consisting of SeP or a series of such peptides, C-terminal peptide of SeP comprising amino acids 260-362 of SeP, peptide having SEQ ID NO: 4, or an amino acid sequence with deletions, substitutions or partial sequences of the above peptides to a patient having an abnormality in synaptic formation, or in acetylcholine receptor function, or in neurotic activity by nitrogen monoxide.

20. The specification of the instant application teaches that selenocysteine-containing proteins are plasma proteins, which encompass full-length SeP of SEQ ID NO: 1, and other diverse proteins derived from SeP, such as a C-terminal peptide, that are involved in the inhibition of cell-death (page 14, lines

15-19; page 8, lines 12-16). The specification also teaches that, SeP induces synaptic formation and differentiation to neurons after 3 days of culture of NG108-15 hybridoma cells (page 21-24, Example 1, Table 1, Figure 1). The specification further teaches that injections of SeP and pilocarpine (acetylcholine receptor agonist) to ICR male mice, resulted in an enhanced induction of convulsion, thereby suggesting an effect of SeP on accelerating acetylcholine receptor function (pages 24-26, Example 2, Table 2).

21. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The specification has not shown a relationship between the structure, function, or properties of the claimed genus of selenocysteine-containing proteins. However, in this case, the only factor present in the claim is a recitation of functional activity. There is not even identification of any particular portion of the SeP structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The brief description in the specification of one SeP polypeptide (SEQ ID NO: 1) is not adequate written description of an entire

genus of functionally equivalent polypeptides, which incorporate all fragments, and variants of SeP.

22. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

23. With the exception of the SeP sequences referred to above (SEQ ID NO: 1), the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The *polypeptide itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

25. Therefore, only the SeP polypeptide comprising the amino acid sequence of SEQ ID NO: 1, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

27. Claims 8-17 are rejected under 35 U.S.C. 102(b) as clearly anticipated by Masaki et al., (WO 02/076492, dated 3 October 2002).

28. The claims are drawn to a method for ameliorating any neurotransmission dysfunction disease (for example, myasthenia gravis), by administering a medicament comprising selenocysteine-containing protein (SeP), peptide consisting of SeP or a series of such peptides, C-terminal peptide of SeP comprising amino acids 260-362 of SeP, peptide having SEQ ID NO: 4, or an amino acid sequence with deletions, substitutions or partial sequences of the

above peptides, to a patient having an abnormality in synaptic formation, or in acetylcholine receptor function, or in neurotic activity by nitrogen monoxide.

29. Masaki et al., teach remedies for ameliorating neurodegenerative diseases, comprising agents, wherein the main component is SeP/or peptide(s) of this protein. Because the treatment remedies disclosed by Masaki et al., anticipates the method step of administration of SeP peptide/peptides to a patient to observe the ameliorating effect, Masaki et al., meet the limitations of claims 8-17 of the instant application. Therefore, the invention described in the reference anticipates the instant invention.

Conclusion

30. No claims are allowed.

31. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Link and Xiao, Immunol Rev. 184: 117-128, 2001.
(Reference showing the rat model for myasthenia gravis)

Burkhardt and Kalden, Rheumatol Int 17: 91-99, 1997
(Reference showing animal models for autoimmune diseases, such as myasthenia gravis)

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
16 January, 2007

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER